

**Remarks**

Claims 1-19 were present in the application as filed. By preliminary amendment filed with the initial application papers, claim 6 was canceled and claim 20 was added, thereby resulting in pending claims 1-5 and 7-20. Claims 1-5 were amended in a paper that was filed contemporaneously with the filing of a Request for Continued Examination under 37 C.F.R. §1.114 to remove the finality of a final Office Action mailed July 7, 2003. In response to a non-final office action mailed February 18, 2004, claim 1 was amended and claim 20 was canceled. Claims 1-5 and 7-19 remain pending in the application.

Claim 1 is amended herein to clarify the nature of the properties of the pharmaceutical drug or vaccine, the alteration of which the use of ionic surfactant seeks to avoid. Accordingly, claim 1 recites a method comprising treating a pharmaceutical drug or vaccine with a concentration of an ionic surfactant that is effective to dissociate the endotoxin from the amphiphilic pharmaceutical drug or vaccine *without adversely affecting the ability of the drug or vaccine to be retained by a filter*. Support for the amendment is found in the specification on page 6, 2nd full paragraph.

Claim 1 is further amended to reflect that following filtration, the amount of ionic surfactant remaining in said solution is *less than 0.002%*. Support for this amendment is found in the specification at page 17, 1<sup>st</sup> full paragraph.

**Rejection Under 35 USC §112, 2nd paragraph**

Claims 1-5 and 7-19 are rejected under USC §112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action alleges that claim 1 is rendered vague and indefinite by the use of the phrase, “without adversely affecting the properties of the drug or vaccine including its ability to be retained by a filter...” Accordingly, claim 1 is amended above to clarify that, for the method of the present invention, it is important that the ionic surfactant not adversely effect the

ability of the drug or vaccine substance to be retained by a MWCO filter. Applicants believe that one of skill in the art would recognize that the ability of the drug or vaccine substance to be retained by a MWCO filter is a function of its size and that this is one property which would be adversely impacted when a surfactant, even a non-denaturing one, disrupts, for example, the quaternary structure of a molecule such as influenza viral antigens, HA and NA. Disruption of a polymeric substance into its subunits not only reduces the size of the molecule, but frequently negatively impacts on other properties, for example, biologic activity, antigenicity etc. Specific support for this amendment is found in the specification on page 6, 2<sup>nd</sup> full paragraph. Applicants respectfully request withdrawal of the rejection based on indefiniteness.

Rejection Under 35 USC §112, 1<sup>st</sup> paragraph

Claims 1-5 and 7-19 are rejected as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Office Action incorrectly states that the phrase, “without adversely affecting the properties of the drug or vaccine including its ability to be retained by a filter...” does not appear in the specification. The language, however, does appear in slightly different form in the specification on page 6, 2<sup>nd</sup> full paragraph.

Applicants’ invention provides a method of removing bacterial endotoxin from an amphiphilic pharmaceutical drug or vaccine. As discussed above, for some vaccines, for example, viral antigens like influenza virus hemagglutinin (HA), which occur in multimeric structures called “rosettes,” maintenance of the quaternary structure of the antigen is important. Endotoxin, however, becomes strongly associated with the hemagglutinin and even becomes incorporated into the rosettes (pages 2-3). The challenge, therefore, is to dissociate the endotoxin from the vaccine without adversely affecting the vaccine’s conformation, and,

therefore, its ability to be retained by a filter with a MWCO cut-off based on the intact multimeric structure.

In this case, Applicants discovered that they could treat a process solution with an ionic, preferably anionic surfactant, and dissociate the endotoxin from the amphiphilic drug or vaccine substance without compromising the structure of the drug or vaccine itself. With the structure of the drug or vaccine preserved, its ability to be retained by the filter is also retained. The resulting solution is then subjected to ultrafiltration such that the larger amphiphilic drug or vaccine complex is retained by the filter, while the smaller, dissociated endotoxin fragments and surfactant pass through the filter.

The claims are further rejected under 35 USC §112, 1<sup>st</sup> paragraph, with respect to the phrase, “and wherein the amount of ionic surfactant remaining in said solution is less than 0.01%.” Claim 1 is amended herein to recite “and wherein the amount of ionic surfactant remaining in said solution is less than 0.002%.” This specific amount appears in the specification on page 17, 1<sup>st</sup> paragraph. Withdrawal of the rejection is respectfully requested.

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. The dependent claims are believed allowable for the same reasons as the independent claims from which they ultimately depend, as well as for their additional limitations. Should the Examiner require clarification of any of the above, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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A handwritten signature in cursive script, reading "Kathy Smith Dias", is written over a horizontal line.

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